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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,588	12/20/2001	Frederic Andre	SANSYL002	1696

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
06/11/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/019,588	ANDRE ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6-9,11-23,25-33 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6-9,11-23,25-33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of request for continued examination under 37 CFR 1.114, amendment and remarks filed 3/16/07. Claim 1 is amended. Claims 1, 3, 6-9,11-23, 25-33 and 35 are pending.

Response to Arguments

Rejections/objections that are not reiterated herein are withdrawn.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/14/07 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Claims 13 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 depends on claim 20, which in the line of dependencies goes back to claim 1, which is directed to a coated dosage form that contains active agent in the matrix. It is thus unclear how the claim 23 does not contain active agent in the matrix. Claim 23 is not rejected over art in view of the indefiniteness of the claim.

Claim 13 is confusing because the dosage form is "compromising," and it is uncertain how the dosage form "compromises."

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1 and 6 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bradbury et al. (US 6,124,362).

Bradbury teaches a composition that can be administered topically, orally or parenterally (column 5, lines 45-55); the composition comprises triterpenes (columns 6 and 7) such as betulinic acid (column 7, lines 37-54; column 8, lines 46-65; column 9, lines 12-26 and Examples 6 and 7) and carrier vehicle such as water, lipophilic or hydrophilic emollients/humectants, surfactants, thickeners, powders, polymers, resins, plasticizers, fillers, lubricants, binders, disintegrants, solvents, co-solvents, buffer systems, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes and pigments (column 12, lines 41-46). Surfactants are desirable and used at levels of 0.1% to 30% and the surfactants are anionic, cationic, non-anionic or amphoteric or combinations (column 15, lines 59-65) and the amphoteric surfactants encompassing zwitterionic surfactants (column 18, lines 27-29). Examples of amphoteric or zwitterionic surfactants used in the composition of Bradbury are the betaines and cocamidopropyl betaine is specifically named (column 18, lines 50-64). The polymers preferred for use in the composition are HPMC alone or in combination with carboxymethylcellulose, acrylic resins, ethylcellulose and polyvinylpyrrolidone (column 22, lines 50-57). The composition also optionally contains enhancers at levels of 0.01% to about 15% (column 22, line 61 to column 23 line 3). Non-steroidal anti-inflammatory actives (NSAIDs) (column 23, lines 57-63) such as acetyl salicylic acid, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid (column 26, lines 6-11) are useable in the composition. The composition is prepared by mixing the ingredient together. The instant application uses solution of polymer to coat the drug according to page 12, lines 8-13), which reads on mixing the drug

with suspension or solution containing the polymer, flavoring agents or fillers (columns 29 and 30) and in the process the active agents, betulinic acid and other actives such as NSAID are coated with the carrier vehicle. Therefore, Bradbury teaches coated drugs, which the coating comprising polymer and surfactants such as the betaine surfactants meeting the requirements of claims 1. Cocamidopropyl betaine, a specific named betaine meets claim 6; delayed release is achieved by the type of the polymer associated with the drug/active in the composition and in the is case, the presence of acrylic type polymer such as the EUDRAGIT polymers meet that limitation. In the alternate, specific zwitterionic surfactants are named by Bradbury to include betaines (column 18, line 48) and specific betaines such as coco dimethyl carboxymethyl betaine, lauryl dimethyl carboxymethyl betaine, lauryl dimethyl alpha-carboxyethyl betaine, cetyl dimethyl carboxymethyl betaine, cetyl dimethyl betaine (available as Lonzaine 16SP from Lonza Corp.), lauryl bis-(2-hydroxyethyl) carboxymethyl betaine, oleyl dimethyl gamma-carboxypropyl betaine, lauryl bis-(2-hydroxypropyl)alpha-carboxyethyl betaine, coco dimethyl sulfopropyl betaine, lauryl dimethyl sulfoethyl betaine, lauryl bis-(2-hydroxyethyl) sulfopropyl betaine, amidobetaines and amidosulfobetaines (wherein the $RCONH(CH_2)_3$ radical is attached to the nitrogen atom of the betaine), oleyl betaine (available as amphoteric Velvetex OLB-50 from Henkel), and cocamidopropyl betaine (available as Velvetex BK-35 and BA-35 from Henkel named are named (column 18, lines 50-64). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made use any of the betaine surfactants named in Bradbury either as an emulsifying agent or thickener or as surfactant that does not irritate the skin or mucous membrane.

7. Claims 1, 3, 6, 7, 9, 13, 14, 16, 18, 29-32 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury et al. (US 6,124,362) in view of Morella et al. (US 6,197,348).

Bradbury teaches a composition that can be administered topically, orally or parenterally (column 5, lines 45-55); the composition comprises triterpenes (columns 6 and 7) such as betulinic acid (column 7, lines 37-54; column 8, lines 46-65; column 9, lines 12-26 and Examples 6 and 7) and carrier vehicle such as water, lipophilic or hydrophilic emollients/humectants, surfactants, thickeners, powders, polymers, resins, plasticizers, fillers, lubricants, binders, disintegrants, solvents, co-solvents, buffer systems, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes and pigments (column 12, lines 41-46). Surfactants are desirable and used at levels of 0.1% to 30% and the surfactants are anionic, cationic, non-anionic or amphoteric or combinations (column 15, lines 59-65) and the amphoteric surfactants encompassing zwitterionic surfactants (column 18, lines 27-29). Examples of amphoteric or zwitterionic surfactants used in the composition of Bradbury are the betaines and cocamidopropyl betaine is specifically named (column 18, lines 50-64). The polymers preferred for use in the composition are HPMC alone or in combination with carboxymethylcellulose, acrylic resins, ethylcellulose and polyvinylpyrrolidone (column 22, lines 50-57). The composition also optionally contains enhancers at levels of 0.01% to about 15% (column 22, line 61 to column 23 line 3). Non-steroidal anti-inflammatory actives (NSAIDs) (column 23, lines 57-63) such as acetyl salicylic acid, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid (column 26, lines 6-11) are useable in the composition. The

composition is prepared by mixing the ingredient together. The instant application uses solution of polymer to coat the drug according to page 12, lines 8-13, which reads on mixing the drug with suspension or solution containing the polymer, flavoring agents or fillers as described in Bradbury at columns 29 and 30, and in the process the active agents, betulinic acid and other actives such as NSAID are coated with the carrier vehicle. Therefore, Bradbury teaches coated drugs, which the coating comprising polymer and surfactants such as the betaine surfactants meeting the requirements of claims 1 and 13. Cocamidopropyl betaine, a specific named betaine meets claim 6; delayed release is achieved by the type of the polymer associated with the drug/active in the composition and in the is case, the presence of acrylic type polymer such as the EUDRAGIT polymers meet the limitation of claims 1. The presence of the NSAIDs, and specifically, acetyl salicylic acid, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid, which are named NSAIDs meet claim 7. The amount of the surfactant at levels of from about 0.1% to about 15% renders obvious the claimed amount of from 10% to 50% since a points within the disclosed range of 0.1% to 15% touches points within the claimed range of from 10% to 50%. When the composition contains HPMC or polyvinylpyrrolidone as described by Bradbury, then claims 11 and 22 are met. When the composition is made into a tablet, claims 9 and 14 are met. When the composition contains buffering agent such as potassium acetate, boric carbonic, phosphoric, succinic, malic, tartaric, citric, acetic, benzoic, lactic, glyceric, gluconic, glutaric or glutamic acid (column 22, lines 15-17) and cocamidopropyl betaine, then claims 29-32 are met.

Claim 18 recites the properties of the composition so that Bradbury's composition inherently has those properties.

While Bradbury discloses the composition of claim 1 having acrylic polymer, Bradbury does not teach the acrylic polymer of the type recited in claim 3. However, Morella describes coating drug cores with acrylic polymers such EUDRAGIT RS100 or EUDRAGIT RL100 (abstract; column 2, line 63 to column 3 line 17; column 4, lines 48-62). Some of the drugs in the coated core are naproxen, diclofenac sodium, ibuprofen, ketoprofen, valproic acid and indomethacin (column 3, lines 47-52). Some of these drugs are the same as those taught in Bradbury such as ibuprofen, naproxen and ketoprofen. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to coat drug particles such as combination of betulinic acid with ibuprofen, naproxen or ketoprofen with acrylic polymer of the types described in Morella and expect sustained release taste masked dosage form.

8. Claims 1, 3, 6-9 and 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heinicke et al. (US 5,834,024) in view of Baichwal et al. (US 5,478,574) and further in view of Niemiec et al. (US 2002/0077256 A1).

Heinicke discloses a diltiazem tablet formulation comprising a core that is a sphere, bead or seed of an inert ingredient and the core comprises a pharmaceutical (diltiazem), a binder, emulsifier or stabilizer and the core may further include a dispersing agent, glidant and/or surfactant (column 4, lines 27-49). In example 1, the core is made up of diltiazem, hydroxypropylcellulose and sugar spheres, the core coated with EUDRAGIT RL and EUDRAGIT RS. Regarding the delayed nature of the instant formulation as recited in claim 1, the formulation of the prior art would also be a delayed release composition since the prior art

teaches the same polymers and would thus inherently produce a timed pulse release of the active agent. The presence of the hydroxypropylcellulose separates diltiazem from the polymer coating layer meeting claim 11. The EUDRAGIT RL (type A) and/or EUDRAGIT RS (type B) coated dosage form meets claim 3. Claims 15-17 are product by process claims while claim 18 recites properties of the dosage form so that the Heinicke dosage from meets claims 15-18. Heinicke tablet dosage form comprising a core that is sphere, bead or seed of an inert ingredient and the core comprises a pharmaceutical (diltiazem) and meets claims 8 and 9, and in the absence of factual evidence, the particle size recited in claim 8 is not inventive over a generic teaching of particles in the prior art.

However, while Heinicke describes a dosage form that contains generic surfactant, Heinicke does not describe the surfactant as amphoteric/zwitterionic or non-ionic or ionic. But, Baichwal describes controlled release dosage form that is a tablet or capsule or pellet (column 10, lines 1-5); Baichwal formulates the dosage form using a wide variety of pharmaceutically active agents (column 11, lines 1 and 2); diltiazem is a named vasodilator in Baichwal (column 11, lines 14 and 15); the dosage form contains wetting agent or surfactants in from about 1 to about 10% or higher by weight (column 8, lines 26-39); the surfactant is anionic or cationic or non-ionic or amphoteric/amphipathic/amphophilic (column 8, lines 4-52); suitable amphoteric/amphipathic/amphophilic surfactants are N-substituted alkyl amides, N-alkyl betaines, sulfobetaines and N-alkyl β-aminopropionates (column 8, lines 57-60). Also, Niemiec teaches the use of amphoteric surfactants such as cocamidopropyl betaine in compositions containing diltiazem (paragraphs [0097], [0100], [0101] and [0171] and claims 16 and 17).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the diltiazem dosage form of Heinicke using surfactant as wetting agent. One having ordinary skill in the art would have been motivated to use the betaine amphoteric/amphipathic/amphophilic surfactant of Baichwal and to further use the specific betaines taught in Niemiec with the expectation of stabilizing or wetting the core or obtaining multiphasic sustained release of the diltiazem active.

9. Claims 1, 3, 7-9, 11-22, 25-33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrieu et al. (US 5,589,190) in view of Wilson et al. (6,403,597) and further in view of Smith et al. (US 5,922,341).

Andrieu discloses pharmaceutical composition comprising alfuzosin hydrochloride core that is coated with methacrylic acid copolymer (EUDRAGIT S) (abstract; column 1, line 51). The formulation comprises tablets that afford immediate or sustained release or microparticles that provide immediate release of alfuzosin (columns 1-3 and claims 1-10). EUDRAGIT S is type B such that Andrieu meets claims 1 and 3. The tablet of Andrieu contains microparticles of polyvinylpyrrolidone in the core with the alfuzosin (column 1, lines 34-46 and Examples 1-3) meeting claims 8, 9, 13 and 14 and in the absence of factual evidence/unexpected results/unusual results, the recited particle size is not inventive over the particles of Andrieu ; the presence of the pyrrolidone meets claims 11 and 12 while the coated core meets the requirements of claims 1 and 13. Example 3 describes a capsule dosage form that contains multiple forms, immediate and delayed/sustained release forms, meeting claim 19-22, 25-28 and 35. Claims 15-17 are product by process claims such that the dosage of Andrieu meets the product of claims 15-17. Claim 18 recites the properties of the dosage form.

Wilson teaches sustained release (column 7, line 63) composition that contains active agents, excipients, surfactants and optional enhancer (abstract; column 5, lines 34-41). The primary active agent is a phosphodiesterase inhibitor (column 8, lines 36-42). A variety of other agents are administered with the inhibitor (column 11, lines 49); the composition is formulated into tablets that contain binders such as polyvinylpyrrolidone to ensure that the tablet remains intact (column 15, 5-15), anionic or cationic or amphoteric or non-ionic surfactants (column 15, lines 5 and 33-35). The composition of Wilson also contains organic acids such as oxalic acid, fumaric acid, malic acid, tartaric acid and citric acid (column 13, lines 64-67). Alfuzosin is one of the few adrenergic antagonists listed at column 12, lines 37 and 40. Similarly, Smith discloses sustained release dosage form that comprises alfuzosin adrenergic antagonist (column 5, lines 55 and 58), organic acid such as maleic acid, fumaric acid, tartaric acid, citric acid or succinic acid (column 6, lines 23-28), and amphoteric surfactant (column 7, lines 62-64).

Andrieu fails to teach the presence of surfactant in the alfuzosin formulation. However, Wilson and Smith teach formulations that comprise alfuzosin and amphoteric surfactant (abstract; column 5, lines 39-44; column 6, 1-5 and column 12, line 40). Wilson and Smith are thus relied upon for the teaching that alfuzosin formulations can have zwitterionic/amphoteric surfactants. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare alfuzosin formulation as disclosed by Andrieu. One having ordinary skill in the art would have been motivated to incorporate amphoteric surfactant in the alfuzosin formulation with the expectation that the presence of the surfactant would facilitate the dissolution of alfuzosin.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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